PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 January 2002 (08.01.02)	
International application No. PCT/CA00/00614	**Applicant's or agent's file reference** 3557-001PCT
International filing date (day/month/year) 26 May 2000 (26.05.00)	**Priority date** (day/month/year) 09 September 1999 (09.09.99)
Applicant MENDEZ, Ivar	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 April 2001 (09.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

ALi SOLEIMAN

Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
G. RONALD BELL & ASSOCIATES
Attn. WALTER, Robert H.
P.O. Box 2450, Station D
K1P 5W6 Ottawa, Ontario
CANADA

Applicant's or agent's file reference 3557-001PCT	Date of mailing *(day/month/year)* 10/10/2000
International application No. PCT/CA 00/00614	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant QUEEN ELIZABETH II, HEALTH SCIENCES CENTRE et al.	International filing date *(day/month/year)* 26/05/2000

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nathalie Geisler

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
3557-001PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00614	26/05/2000	09/09/1999
Applicant		
QUEEN ELIZABETH II, HEALTH SCIENCES CENTRE et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[X] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No:
PCT/CA 00/00614

A. CLASSIFICATION OF SUBJECT MATTER
A61M5/00,5/31,5/315,5/46,7/00,A61B17/00,19/00

According to International Patent Classification (IPC) or to both national classification and IPC[7]

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B,A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/44079 A1 (ELEKTA AB) 27 Novmeber 1997, the whole document, especially figs. 1-3, abstract, page 1, lines 1-12, page 1, line 27 - page 2, line 2, page 3, line 32 - page 4, line 25, page 5, line 19 - page 6, line 17, page 7, line 20 - page 8, line 10, claims 1,8.	1,6,11
A	US 5792110 A (CUNNINGHAM) 11 August 1998, the whole document, especially figs. 1A,1B,3A-3C, 5-7C, column 7, line 55 -	1,6

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search
28 August 2000

Date of mailing of the international search report
10 10 2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL – 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
LUDWIG

Form PCT/ISA/210 (second sheet) (July 1992)

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	column 8, line 29, column 9, line 56 - column 11, line 52. (cited in the application)	
A	ADVANCES AND TECHNICAL STANDARDS IN NEUROSURGERY vol. 23, 1997, pages 3-46 REHNCRONA S. et al.: ' A Critical Review of the Current Status and Possible Developments in Brain Transplantation', page 9, last paragraph - page 12, first paragraph (cited in the application).	1,12
A	NEUROSURGERY vol. 36, no. 5, May 1995, pages 1044-1048 BREEZE R.E. et al.: 'IMPLANTATION OF FETAL TISSUE FOR THE MANAGEMENT OF PARKINSON'S DISEASE: A TECHNICAL NOTE', the whole article (cited in the application).	1,12
A	NEUROSCIENCE, vol. 63, no. 1, 1994, pages 57-72 NIKKHAH G. et al.: 'A MICROTRANSPLANTATION APPROACH FOR CELL SUSPENSION GRAFTING IN THE RAT PARKINSON MODEL: A DETAILED ACCOUNT OF THE METHODOLOGY', page 58, 3rd paragraph - page 60, 4th paragraph (cited in the application).	1

ANHANG

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

ANNEX

To the International Search Report to the international Patent Application No.

ANNEXE

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/CA 00/00614 SAE 285455

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This annex lists the patent family members relating to the patent documents cited in the above-mentioned search report. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La presénte annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visée ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsibilité de l' Office.

Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9744079	27-11-1997	AU A1 21874/97	09-12-1997
		EP A1 902699	24-03-1999
		SE A0 9601974	23-05-1996
		SE A 9601974	13-10-1997
		SE C2 505822	13-10-1997
US A 5792110	11-08-1998	AU A1 35768/97	14-01-1998
		CA AA 2259214	31-12-1997
		EP A1 915716	19-05-1999
		WO A1 9749443	31-12-1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17585 A1

(51) International Patent Classification[7]: A61M 5/00, 5/31, 5/315, 5/46, 7/00, A61B 17/00, 19/00

(21) International Application Number: PCT/CA00/00614

(22) International Filing Date: 26 May 2000 (26.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,282,007 9 September 1999 (09.09.1999) CA

(71) Applicant *(for all designated States except US)*: QUEEN ELIZABETH II, HEALTH SCIENCES CENTRE [CA/CA]; 1278 Tower Road, Halifax, Nova Scotia B3H 2Y9 (CA).

(72) Inventor; and

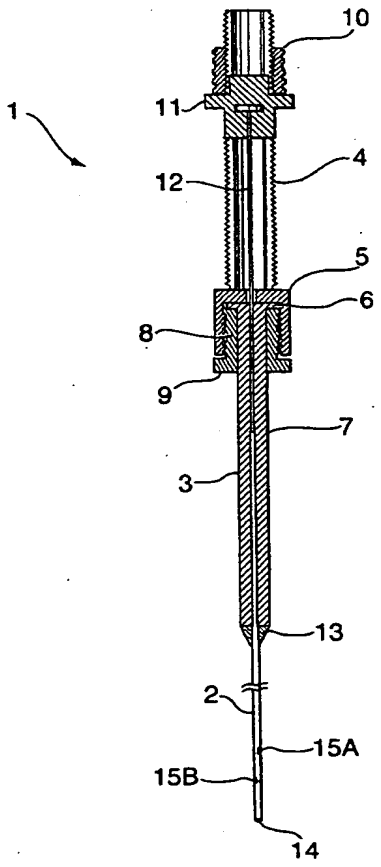
(75) Inventor/Applicant *(for US only)*: MENDEZ, Ivar [CA/CA]; Queen Elizabeth II, Health Sciences Centre, New Halifax Infirmary, 1796 Summer Street, Room 3806, Halifax, Nova Scotia B3H 3A7 (CA).

(74) Agent: WALTER, Robert, H.; G. Ronald Bell & Associates, P.O. Box 2450, Station D, Ottawa, Ontario K1P 5W6 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: NEURAL TRANSPLANTATION DELIVERY SYSTEM



(57) Abstract: A device and method for neural transplantation in the human brain comprising a microinjector (1), transplantation cannula (2) and bullet guide (16) is disclosed. The microinjector (1) is designed to connect to the proximal end of a syringe barrel (7) and plunger (12) while the transplantation cannula (2) interfaces with the distal end of the syringe barrel (7). In combination, the microinjector (1) and transplantation cannula (2) permit the delivery of multiple cell grafts in a three-dimensional array using a unique spiral technique. The bullet guide (16), which is attachable to a commercially available stereotactic frame, is a multiple channel adapter that functions as a mechanical guiding system for the transplantation cannula (2) and permits plural, spaced deployment of the cannula (2) without adjusting or disturbing the frame.

WO 01/17585 A1

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Intern al Application No:
PCT/CA 00/00614

A. CLASSIFICATION OF SUBJECT MATTER
A61M5/00,5/31,5/315,5/46,7/00,A61B17/00,19/00

According to International Patent Classification (IPC) or to both national classification and IPC[7]

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B,A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 97/44079 A1 (ELEKTA AB) 27 Novmeber 1997, the whole document, especially figs. 1-3, abstract, page 1, lines 1-12, page 1, line 27 - page 2, line 2, page 3, line 32 - page 4, line 25, page 5, line 19 - page 6, line 17, page 7, line 20 - page 8, line 10, claims 1,8. --	1,6,11
A	US 5792110 A (CUNNINGHAM) 11 August 1998, the whole document, especially figs. 1A,1B,3A-3C, 5-7C, column 7, line 55 -	1,6

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search
28 August 2000

Date of mailing of the international search report
10. 10. 2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL – 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	NEUROSURGERY vol. 36, no. 5, May 1995, pages 1044-1048 BREEZE R.E. et al.: 'IMPLANTATION OF FETAL TISSUE FOR THE MANAGEMENT OF PARKINSON'S DISEASE: A TECHNICAL NOTE', the whole article (cited in the application).	1,12
A	NEUROSCIENCE, vol. 63, no. 1, 1994, pages 57-72 NIKKHAH G. et al.: 'A MICROTRANSPLANTATION APPROACH FOR CELL SUSPENSION GRAFTING IN THE RAT PARKINSON MODEL: A DETAILED ACCOUNT OF THE METHODOLOGY', page 58, 3rd paragraph - page 60, 4th paragraph (cited in the application).	1

INTERNATIONAL SEARCH REPORT

ANHANG : ANNEX ANNEXE

Zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

To the International Search Report to the international Patent Application No.

Au rapport de recherche international relativ à la demande de brevet international n°

PCT/CA 00/00614 SAE 285455

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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Im Recherchenbericht angeführte Patentdokumente Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9744079	27-11-1997	AU A1 21874/97	09-12-1997
		EP A1 902699	24-03-1999
		SE A0 9601974	23-05-1996
		SE A 9601974	13-10-1997
		SE C2 505822	13-10-1997
US A 5792110	11-08-1998	AU A1 35768/97	14-01-1998
		CA AA 2259214	31-12-1997
		EP A1 915716	19-05-1999
		WO A1 9749443	31-12-1997

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 12

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3557-001PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00614	26/05/2000	09/09/1999
International Patent Classification (IPC) or national classification and IPC A61M5/00		
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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 14 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/04/2001	28.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rosenblatt, T Telephone No. +49 89 2399 8732

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00614

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-5,10-16,18,19, 21-26	as originally filed			
6-9,9a,17,20, 20a	as received on	22/10/2001	with letter of	18/10/2001

Claims, No.:

1-20	as received on	22/10/2001	with letter of	18/10/2001

Drawings, sheets:

1/9-9/9	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 15-20.

because:

   ☒ the said international application, or the said claims Nos. 15-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 19,20.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.
   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item I
Basis of the report

1. The amendments filed with the letter dated 18.10.2001 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

1.1 The applicant replaced in claim 2 the feature **driving nut** by the more general feature **driving means**. The originally filed application documents only disclose a driving nut and no other suitable "means". Hence the generalisation of the feature driving nut is not justified and constitutes an addition of subject-matter. A corresponding unallowable amendment has been introduced in page 17, line 2.

1.2 Also applicant introduced on amended pages 20 and 20a a passage bridging the pages, which extends beyond the content of the application as filed. The originally filed application documents did not suggest any other embodiments or modifications.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The subject-matter of independent claim 15 and its dependent claims 16 to 18 relates to a method of using a neural transplantation device and comprises the steps of sequential delivery of contents of a syringe barrel at a predetermined neural target site. Hence this method relates to the treatment of the human or animal body by therapy and surgery (Rule 67.1(iv) PCT). According to Art. 34(4)(a)(i) PCT this International Preliminary Examination Authority does not go into the questions referred to in Art. 33(1) PCT.

   Furthermore it is noted that the subject-matter of claims 15 to 18 was not subject to search, since the claims were only filed after the first written opinion.

2. It is also noted with reference to independent claim 19 and its dependent claim 20, which refer to a bullet guide, that originally these claims were formulated as

dependent claims. Since the International Search Authority did not find any novelty destroying or otherwise highly relevant document for the originally filed independent claim 1, the search was not further performed for bullet guides *per se*. The indication given in the International Search Report for the document of authors S. REHNCRONA and R.E. BREEZE, for original claim 12 (neural transplantation device comprising a bullet guide) is only given as information to the applicant but does not mean that a search for bullet guides *per se* had been performed (see PCT International Search Guidelines, III-3.8, from third sentence onwards, PCT Gazette from 18.10.1998, Section IV).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Nearest prior art to the subject-matter of claim 1 is the neural transplantation system known from document D1 = US-A-5 792 110. The subject-matter of claim 1 is in particular distinguished by the presence of a pair of side port holes diametrically opposed and slightly offset to each other. The subject-matter of claim 1 therefore is new within the meaning of Art. 33(2) PCT.

   The subject-matter of claim 1 is also considered to meet the requirement of inventive activity (Art. 33(3) PCT), since the distinguishing feature is not obviously derivable from the available prior art. It provides for the advantage of minimizing brain trauma while maximizing cell graft deposits. None of the prior art documents cited in the international search report teaches this feature.

2. Claims 2 to 14 are dependent on claim 1 and therefore also meet the requirements of Art. 33(2) and (3) PCT.

3. The neural transplantation device according to claims 1 to 14 may be produced industrially and commercialised, so that the conditions of Art. 33(4) PCT are also met.

minimal number of penetrations into the host brain.

Another object of the present invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, which permits the precise placement of a predetermined amount of neural cells or tissue to a targeted site in a subject.

Another object of the invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, that can be easily incorporated with a syringe to facilitate reliable and safe neural transplantation of cell grafts to the human brain.

A further object of the invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, which in combination with a syringe, are designed to minimize implantation tissue trauma and maximize the number of graft deposits per injection using a unique spiral technique.

Still another object of the invention is to provide a bullet guide which, when mounted to a stereotactic frame, functions as a mechanical guiding system for the transplantation cannula thereby permitting multiple access of the cannula without adjusting or disturbing the frame.

According to one aspect of the invention there is provided a neural transplantation device which comprises:

(a) a syringe including a syringe barrel and plunger;
(b) a microinjector adapted for connection to the proximal end of the syringe barrel and for cooperation with the plunger for effecting incremental depression and retraction of the plunger; and

(c) a cannula adapted for connection to the distal end of the syringe barrel, said cannula having a blunt closed lower end and being formed with a pair of offset port holes on opposite sides of the cannula for fluid delivery;

characterized in that upon placement of the cannula in a targeted cerebral site, operation of the microinjector to effect incremental depression of the plunger results in metered injection of fluid from the syringe barrel through the cannula holes to a targeted site.

A particular embodiment provides a microinjector and neural transplantation cannula for use in combination with a syringe, comprising:

(a) a longitudinal cylindrical sleeve which extends into a cylindrical barrel of larger diameter at the distal end thereof;

(b) a guide nut adjustably rotated within the cylindrical barrel and adapted to cooperate with the proximal end of a syringe barrel;

(c) a drive nut rotatably mounted on the cylindrical sleeve and adapted to engage with a plunger driver rotatably mounted on the cylindrical sleeve and cooperating with both the drive nut and a syringe plunger; and

(d) a hollow cannula which is closed at its extreme distal end and has a pair of port holes near the distal end that are diametrically opposed and slightly offset to each other;

characterized in that placement of the transplantation cannula in contact with a targeted cerebral site followed by rotation of the drive nut renders a downward axial force to the plunger of the syringe thereby aspirating the fluid contents of the syringe barrel from the holes to effect delivery of an injection; followed by rotation of the guide nut in the opposite direction to move the syringe in an upward vertical direction to allow repositioning of the cannula for subsequent delivery of injection fluid; and

rotating the drive nut and guide nut in a repeated sequential manner to distribute multiple portions of injection fluid in a three-dimensional spiral array at predetermined injection sites with a single penetration of the cannula.

Another aspect of the invention provides a bullet guide for use in combination with a stereotactic frame which functions as a mechanical guiding system for the transplantation cannula, the bullet guide comprising:

(a) a top portion comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes sized to accommodate the insertion of the cannula; and

(b) a bottom portion comprising a hollow cylindrical element of the same diameter as the top portion but having a longer longitudinal axis; said portion being closed at both ends and each end having an array of equidistantly spaced holes sized to accommodate the insertion of the cannula;

characterized in that the top portion and bottom portion are mounted in spaced coaxial alignment, in a stereotactic frame with the respective arrays of holes in mutual alignment to guide deployment of the cannula through an aligned pair of said holes to a predetermined cerebral target.

Thus, the present invention affords a microinjector and transplantation cannula adapted and designed for use, for instance, with a 50 μl Hamilton syringe. The Hamilton syringe comprises a syringe barrel, which receives fluid contents, and a rod-like plunger for expelling the fluid contents from the barrel. In the assembled relationship, the microinjector and cannula create a secure and cooperative attachment to the extreme proximal and distal ends, respectively, of a Hamilton syringe, such that all

the components are coaxially aligned to one another.

The microinjector essentially comprises a longitudinal cylindrical sleeve which is threaded on its exterior surface and extends abruptly into a plunger guide at its distal end that has a larger diameter than the sleeve. The exterior surface of the plunger guide is uniform and its internal diameter is sized to fit and cooperate with the peripheral shoulder of the barrel of a syringe. The inner wall of the plunger guide is threaded to match and interface with a guide nut which is adjustably rotated inside the barrel. The guide nut is a small hollow cylindrical spool with a collar at its extreme distal end that acts as a lower boundary stop to limit its position inside the plunger guide when fully wound. In turn, the guide nut is designed to securely interface with the syringe immediately beneath the peripheral shoulder located at the extreme proximal end of the barrel. Accordingly, attaching the guide nut to the barrel converts the syringe to an adjustably rotated device that can easily be wound inside the plunger guide. Therefore, rotating the guide nut in either a clockwise or counter-clockwise direction simultaneously rotates the syringe in the same direction. Depending on the direction of rotation, this operation ultimately translates into either an upward or downward vertical movement of the syringe. Therefore, the vertical distance in which the syringe moves by rotation of the guide nut is a function of the length and diameter of the plunger guide and guide nut.

Mounted at the proximal end of the cylindrical sleeve is a threaded drive nut engaged with a threaded plunger driver which are both adjustably rotated in either a clockwise or counter-clockwise direction. As a result of their connection, rotating one element moves the other element simultaneously. The plunger driver is engaged with the proximal end of a syringe plunger such that when the driver

Mounted at the proximal end of the cylindrical sleeve (4) is a threaded drive nut (10) engaged with a threaded plunger driver (11) which are both adjustably rotated in either a clockwise or counter-clockwise direction. As a result of their connection, rotating either the drive nut (10) or plunger driver (11) moves the other element simultaneously. The plunger driver (11) is engaged with the proximal end of a syringe plunger (12) such that when the driver (11) is rotated, the movement of the plunger (12) is controlled in either an upward or downward direction along a longitudinal axis parallel to the syringe (3). Therefore, during neural transplantation, rotation of the plunger driver (11) results in delivery of a desired volume of cell suspension contained within the syringe barrel (7).

The transplantation cannula (2) is a long narrow needle provided with a standard Luer lock (13) at its proximal end. The Luer lock (13) allows the cannula (2) to be readily attached to and in fluid connection with the contents of the syringe (3), and then easily removed following use. The tip of the cannula (2) at the extreme distal end (14) is closed and its outer surface has been rounded and polished in a semi-spherical shape to minimize trauma to neural tissue upon insertion. As shown in Figure 2, located near the tip of the cannula are a pair of holes, (15A) and (15B), to allow egress of cells during aspiration of the syringe (3) and which are diametrically opposed and slightly offset to one another. In the embodiment shown, hole (15B) is located 1.0 mm from the cannula tip (14) and hole (15A) is offset from hole (15B) by a distance of 2.0 mm.

The bullet guide (16), illustrated in Figure 3, comprises both a top portion and a bottom portion that are mounted to a stereotactic frame and function as a mechanical guiding system for the transplantation cannula (2). The top

suspension, the guide nut (8) is rotated 90° in a clockwise position thereby withdrawing the syringe (3) and cannula (2) in an upward vertical direction at a predetermined distance away from the first target site. Aspiration and delivery of the second volume of cell suspension is made by repeating the operation involving rotation of the plunger driver (11). Sequential repetition of the steps involving rotation of the plunger driver (11) and guide nut (8) to deliver the contents of the syringe (3) and reposition the cannula (2), respectively, allows several injections to be made thereby distributing the cells in a three-dimensional spiral array within the brain tissue.

Figures 6A and 6B provide front and top views, respectively, of a sequence of four injections, 3.0 mm apart, made in a single trajectory. The first injection delivers two graft deposits oriented opposite to each other and one at a slightly higher level than the other (solid balls). The cannula (2) is then withdrawn 3.0 mm in a stepwise fashion and rotated 90° clockwise and so that another two deposits can be made (solid balls). The process is repeated two more times until a total of 8 deposits are made per trajectory resulting in a three-dimensional spiral array.

Additional cell deposits at different trajectories are made by removing the microinjector (1) from its operative position, governed by the square grids, (19) and (21), of the bullet guide (16), and then reinserting the transplantation cannula (2) of the microinjector (1) through another specified landmark of holes contained within the grids (19) and (21).

The following Examples illustrate the invention:

CLAIMS:

1. A neural transplantation device comprising:
(a) a syringe including a syringe barrel and plunger;
(b) a microinjector adapted for connection to the proximal end of the syringe barrel and cooperation with the plunger for effecting incremental depression of the plunger; and
(c) a cannula adapted for connection to the distal end of the syringe barrel, said cannula having a blunt closed lower end and being formed with a pair of offset port holes on opposite sides of the cannula for fluid delivery;

characterized in that placement of the cannula in a targeted cerebral site, operation of the microinjector to effect incremental depression of the plunger results in metered injection of fluid from the syringe barrel through the cannula holes to a targeted site.

2. The neural transplantation device according to Claim 1, characterized in that the microinjector and neural transplantation cannula are used in combination with a syringe, comprising:
(a) a longitudinal cylindrical sleeve which extends into a cylindrical barrel of larger diameter at the distal end thereof;
(b) a guide nut adjustably rotated within the cylindrical barrel and adapted to cooperate with the proximal end of a syringe barrel;
(c) a drive nut rotatably mounted on the cylindrical sleeve and adapted to engage with a plunger driver rotatably mounted on the cylindrical sleeve and cooperating with both the drive nut and a syringe plunger; and
(d) a hollow cannula which is closed at its extreme distal end and has a pair of port holes near the distal end that are diametrically opposed and slightly offset to each other;

characterized in that placement of the transplantation cannula in contact with a targeted cerebral site followed

by rotation of the drive nut renders a downward axial force to the plunger of the syringe thereby aspirating fluid contents of the syringe barrel from the port holes to effect delivery of an injection; followed by rotation of the guide nut in the opposite direction to move the syringe in an upward vertical direction to allow repositioning of the cannula for subsequent delivery of injection fluid; and rotating the drive nut and guide nut in a repeated sequential manner to distribute multiple portions of injection fluid in a three-dimensional spiral array at predetermined injection sites with a single penetration of the cannula.

3. The neural transplantation device according to Claim 2, characterized in that an exterior wall of the guide nut and an interior wall of the cylindrical barrel, which receives the guide nut, are threaded such that rotation of the guide nut relative to the cylindrical barrel causes a corresponding linear, axial movement of the guide nut through the cylindrical barrel.

4. The neural transplantation device according to Claim 2 or 3, characterized in that an exterior wall of the longitudinal cylindrical sleeve and an interior wall of both the plunger driver and drive nut are threaded such that rotation of either the plunger driver or drive nut relative to the cylindrical sleeve causes a corresponding linear, axial movement of the plunger driver, the drive nut and the syringe plunger.

5. The neural transplantation device according to any one of Claims 1 to 4, characterized in that the neural transplantation cannula has a length sufficient to linearly penetrate and enter a host brain such that the pair of port holes is concurrently positionable within the host brain.

6. The neural transplantation device according to any one of Claims 1 to 5, characterized in that the transplantation cannula has an outside diameter of about 0.8 mm.

7. The neural transplantation device according to any one of Claims 1 to 6, characterized in that the port holes are positioned such that the distances between a distal edge of the first and second port holes to the distal end of the cannula are about 1.0 mm and 3.0 mm, respectively.

8. The neural transplantation device according to any one of Claims 1 to 7, characterized in that the diameters of the port holes are the same.

9. The neural transplantation device according to Claim 8, characterized in that the diameter of each port hole is 0.3 mm.

10. The neural transplantation device according to any one of Claims 1 to 9, characterized in that the microinjector system is manufactured from acetal nylon and ionized aluminum.

11. The neural transplantation device according to any one of Claims 1 to 10, characterized in that the cannula is manufactured from stainless steel.

12. The neural transplantation device according to any one of Claims 1 to 11, characterized in that a bullet guide is provided for use in combination with a stereotactic frame and which functions as a mechanical guiding system for the cannula, the bullet guide comprising:
(a) a top portion comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes sized to accommodate the insertion of the cannula; and
(b) a bottom portion comprising a hollow cylindrical

element of the same diameter as the top portion but having a longer longitudinal axis; said portion being closed at both ends and each end having an array of equidistantly spaced holes sized to accommodate the insertion of the cannula;

characterized in that the top portion and bottom portion are mounted in spaced coaxial alignment, in a stereotactic frame with the respective arrays of holes in mutual alignment to guide deployment of the cannula through an aligned pair of said holes to a predetermined cerebral target.

13. The neural transplantation device according to Claim 12, characterized in that the top portion and bottom portion of the bullet guide are manufactured from acetal nylon.

minimal number of penetrations into the host brain.

Another object of the present invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, which permits the precise placement of a predetermined amount of neural cells or tissue to a targeted site in a subject.

Another object of the invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, that can be easily incorporated with a syringe to facilitate reliable and safe neural transplantation of cell grafts to the human brain.

A further object of the invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, which in combination with a syringe, are designed to minimize implantation tissue trauma and maximize the number of graft deposits per injection using a unique spiral technique.

Still another object of the invention is to provide a bullet guide which, when mounted to a stereotactic frame, functions as a mechanical guiding system for the transplantation cannula thereby permitting multiple access of the cannula without adjusting or disturbing the frame.

According to one aspect of the invention there is provided a neural transplantation device for use in combination with a syringe, including a syringe barrel and plunger, comprising:

- a microinjector adapted for connection to a proximal end of a syringe barrel and in cooperation with a syringe plunger for effecting incremental depression of the plunger; and
- a cannula adapted for connection to a distal end of the syringe barrel, said cannula having a single passageway with

an open upper end and a lower end defining a blunt closed tip and having a pair of side port holes that are diametrically opposed and slightly offset to each other near the vicinity of the cannula tip;

- whereby upon placement of the cannula at a predetermined targeted neural site, the microinjector is capable of effecting incremental depression of the plunger to result in a metered delivery of the contents of the syringe barrel through the cannula port holes at the targeted site.

A particular embodiment provides a neural transplantation device, characterized in that the microinjector comprises:

- a longitudinal hollow cylindrical sleeve extending into a cylindrical barrel of larger diameter at the distal end thereof, said sleeve capable of receiving a syringe plunger;
- a guide nut rotatably adjustable within the cylindrical barrel and adapted to cooperate with the proximal end of the syringe barrel; and
- a driving means rotatably mounted near the proximal end of the cylindrical sleeve and adapted to cooperate with the syringe plunger;
- whereby operation of the microinjector in combination with the syringe and the cannula allows delivery of an injection such that rotation of the driving means renders a downward axial force to the plunger of the syringe thereby aspirating contents of the syringe barrel through the side port holes of the cannula; while rotation of the guide nut in the opposite direction moves the syringe in an upward axial direction to reposition the cannula; and rotation of the driving means and the guide nut in a repeated manner facilitates sequential delivery of multiple portions of the contents of the syringe barrel along a single trajectory in a three-dimensional spiral array at a predetermined neural injection site.

According to another aspect of the invention, there is

provided a method of using the neural transplantation device for administering an injection, comprising the steps of:

- positioning the syringe plunger in an initial upward position;
- positioning the syringe barrel with attached guide nut in an essentially unwound position inside the cylindrical barrel of the sleeve of the microinjector;
- rotating the driving means to advance the syringe plunger in a downward axial direction through the syringe barrel thereby aspirating and depositing a portion of the contents of the syringe barrel through the side port holes of the cannula;
- rotating the guide nut to effectively withdraw the syringe and cannula in an upward axial direction at a predetermined distance away from a previous neural target site; and
- repeating steps involving rotating the driving means to deliver a portion of the contents of the syringe barrel and rotating the guide nut to reposition the cannula, thereby resulting in sequential delivery of multiple portions of the contents of the syringe barrel in a three-dimensional spiral array per single trajectory at a predetermined neural target site.

Yet according to another aspect of the invention, there is provided a bullet guide for use in combination with a stereotactic frame which functions as a mechanical guiding system for the neural transplantation cannula, the bullet guide comprising:

- a top member comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes sized to accommodate the insertion of the cannula; and
- a bottom member comprising a hollow cylindrical element of the same diameter as the top member but having a longer longitudinal axis; said bottom member being closed at both ends and each end having an array of equidistantly spaced holes sized to accommodate the insertion of the cannula;

- characterized in that the top member and bottom member are mounted in spaced coaxial alignment in the stereotactic frame with the respective arrays of holes in mutual alignment to guide deployment of the cannula through an aligned set of said holes to a predetermined cerebral target.

Thus, the present invention affords a microinjector and transplantation cannula adapted and designed for use, for instance, with a 50 µl Hamilton syringe. The Hamilton syringe comprises a syringe barrel, which receives fluid contents, and a rod-like plunger for expelling the fluid contents from the barrel. In the assembled relationship, the microinjector and cannula create a secure and cooperative attachment to the extreme proximal and distal ends, respectively, of a Hamilton syringe, such that all the components are coaxially aligned to one another.

The microinjector essentially comprises a longitudinal cylindrical sleeve which is threaded on its exterior surface and extends abruptly into a plunger guide at its distal end that has a larger diameter than the sleeve. The exterior surface of the plunger guide is uniform and its internal diameter is sized to fit and cooperate with the peripheral shoulder of the barrel of a syringe. The inner wall of the plunger guide is threaded to match and interface with a guide nut which is adjustably rotated inside the barrel. The guide nut is a small hollow cylindrical spool with a collar at its extreme distal end that acts as a lower boundary stop to limit its position inside the plunger guide when fully wound. In turn, the guide nut is designed to securely interface with the syringe immediately beneath the peripheral shoulder located at the extreme proximal end of the barrel. Accordingly, attaching the guide nut to the barrel converts the syringe to an adjustably rotated device that can easily be wound inside the plunger guide. Therefore, rotating the guide nut in

either a clockwise or counter-clockwise direction simultaneously rotates the syringe in the same direction. Depending on the direction of rotation, this operation ultimately translates into either an upward or downward vertical movement of the syringe. Therefore, the vertical distance in which the syringe moves by rotation of the guide nut is a function of the length and diameter of the plunger guide and guide nut.

Mounted at the proximal end of the cylindrical sleeve is a driving means comprising a threaded drive nut engaged with a threaded plunger driver which are both adjustably rotated in either a clockwise or counter-clockwise direction. As a result of their connection, rotating one element moves the other element simultaneously. The plunger driver is engaged with the proximal end of a syringe plunger such that when the driver

Mounted at the proximal end of the cylindrical sleeve (4) is a driving means comprising a threaded drive nut (10) engaged with a threaded plunger driver (11) which are both adjustably rotated in either a clockwise or counter-clockwise direction. As a result of their connection, rotating either the drive nut (10) or plunger driver (11) moves the other element simultaneously. The plunger driver (11) is engaged with the proximal end of a syringe plunger (12) such that when the driver (11) is rotated, the movement of the plunger (12) is controlled in either an upward or downward direction along a longitudinal axis parallel to the syringe (3). Therefore, during neural transplantation, rotation of the plunger driver (11) results in delivery of a desired volume of cell suspension contained within the syringe barrel (7).

The transplantation cannula (2) is a long narrow needle provided with a standard Luer lock (13) at its proximal end. The Luer lock (13) allows the cannula (2) to be readily attached to and in fluid connection with the contents of the syringe (3), and then easily removed following use. The tip of the cannula (2) at the extreme distal end (14) is closed and its outer surface has been rounded and polished in a semi-spherical shape to minimize trauma to neural tissue upon insertion. As shown in Figure 2, located near the tip of the cannula are a pair of holes, (15A) and (15B), to allow egress of cells during aspiration of the syringe (3) and which are diametrically opposed and slightly offset to one another. In the embodiment shown, hole (15B) is located 1.0 mm from the cannula tip (14) and hole (15A) is offset from hole (15B) by a distance of 2.0 mm.

The bullet guide (16), illustrated in Figure 3, comprises both a top portion and a bottom portion that are mounted to a stereotactic frame and function as a mechanical guiding system for the transplantation cannula (2). The top

suspension, the guide nut (8) is rotated 90° in a clockwise position thereby withdrawing the syringe (3) and cannula (2) in an upward vertical direction at a predetermined distance away from the first target site. Aspiration and delivery of the second volume of cell suspension is made by repeating the operation involving rotation of the plunger driver (11). Sequential repetition of the steps involving rotation of the plunger driver (11) and guide nut (8) to deliver the contents of the syringe (3) and reposition the cannula (2), respectively, allows several injections to be made thereby distributing the cells in a three-dimensional spiral array within the brain tissue.

Figures 6A and 6B provide front and top views, respectively, of a sequence of four injections, 3.0 mm apart, made in a single trajectory. The first injection delivers two graft deposits oriented opposite to each other and one at a slightly higher level than the other (solid balls). The cannula (2) is then withdrawn 3.0 mm in a stepwise fashion and rotated 90° clockwise and so that another two deposits can be made (solid balls). The process is repeated two more times until a total of 8 deposits are made per trajectory resulting in a three-dimensional spiral array.

Additional cell deposits at different trajectories are made by removing the microinjector (1) from its operative position, governed by the square grids, (19) and (21), of the bullet guide (16), and then reinserting the transplantation cannula (2) of the microinjector (1) through another specified landmark of holes contained within the grids (19) and (21).

Although only one exemplary embodiment of this invention has been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiment without materially departing from the

novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses are intended to cover the structures described herein as performing the recited function and not only structural equivalents, but also equivalent structures.

The following Examples illustrate the invention:

CLAIMS:

1. A neural transplantation device for use in combination with a syringe (3), including a syringe barrel (7) and plunger (12), comprising:
- a microinjector (1) adapted for connection to a proximal end of a syringe barrel (7) and in cooperation with a syringe plunger (12) for effecting incremental depression of the plunger (12); and
- a cannula (2) adapted for connection to a distal end of the syringe barrel (7), said cannula (2) having a single passageway with an open upper end and a lower end defining a blunt closed tip (14) and having a pair of side port holes (15A),(15B) that are diametrically opposed and slightly offset to each other near the vicinity of the cannula tip (14);
- whereby upon placement of the cannula (2) at a predetermined targeted neural site, the microinjector (1) is capable of effecting incremental depression of the plunger (12) to result in a metered delivery of the contents of the syringe barrel (7) through the cannula port holes (15A),(15B) at the targeted site.

2. The neural transplantation device according to Claim 1, characterized in that the microinjector (1) comprises:
- a longitudinal hollow cylindrical sleeve (4) extending into a cylindrical barrel (5) of larger diameter at the distal end thereof, said sleeve (4) capable of receiving a syringe plunger (12);
- a guide nut (8) rotatably adjustable within the cylindrical barrel (5) and adapted to cooperate with the proximal end of the syringe barrel (7); and
- a driving means rotatably mounted near the proximal end of the cylindrical sleeve (4) and adapted to cooperate with

the syringe plunger (12);

- whereby operation of the microinjector (1) in combination with the syringe (3) and the cannula (2) allows delivery of an injection such that rotation of the driving means renders a downward axial force to the plunger (12) of the syringe (3) thereby aspirating contents of the syringe barrel (7) through the side port holes (15A),(15B) of the cannula (2); while rotation of the guide nut (8) in the opposite direction moves the syringe (3) in an upward axial direction to reposition the cannula (2); and rotation of the driving means and the guide nut (8) in a repeated manner facilitates sequential delivery of multiple portions of the contents of the syringe barrel (7) along a single trajectory in a three-dimensional spiral array at a predetermined neural injection site.

3. The neural transplantation device according to Claim 2, characterized in that the guide nut (8) is a small hollow cylindrical spool with a collar (9) at its extreme distal end that acts as a lower boundary stop to limit its position inside the cylindrical barrel (5) when fully wound inside.

4. The neural transplantation device according to Claim 2 or 3, characterized in that an exterior wall of the guide nut (8) and an interior wall of the cylindrical barrel (5), which receives the guide nut (8), are threaded such that rotation of the guide nut (8) relative to the cylindrical barrel (5) causes a corresponding linear, axial movement of the guide nut (8) through the cylindrical barrel (5).

5. The neural transplantation device according to any one of Claims 2 to 4, characterized in that the driving means comprises a plunger driver (11) and a drive nut (10).

6. The neural transplantation device according to Claim 5, characterized in that the plunger driver (11) is adapted to cooperate with the proximal end of the syringe plunger (12) and a distal end of the drive nut (10) is engaged with a proximal end of the plunger driver (11), such that rotation of either the drive nut (10) or plunger driver (11) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and syringe plunger (12).

7. The neural transplantation device according to Claim 5 or 6, characterized in that an exterior wall of the longitudinal cylindrical sleeve (4) and an interior wall of the plunger driver (11) and the drive nut (10) are threaded such that rotation of either the plunger driver (11) or drive nut (10) relative to the cylindrical sleeve (4) causes a corresponding linear, axial movement of the plunger driver (11), drive nut (10), and the syringe plunger (12).

8. The neural transplantation device according to any one of Claims 1 to 7, characterized in that the cannula (2) has a length sufficient to linearly penetrate and enter a host brain such that the pair of side port holes (15A),(15B) is concurrently positionable at a predetermined targeted site within the host brain.

9. The neural transplantation device according to any one of Claims 1 to 8, characterized in that the cannula (2) has an outside diameter of about 0.8 mm.

10. The neural transplantation device according to any one of Claims 1 to 9, characterized in that the side port holes (15A),(15B) are positioned such that the distances between a distal edge of a first (15B) and a second side

port hole (15A) to the cannula tip (14) are about 1.0 mm and 3.0 mm, respectively.

11. The neural transplantation device according to any one of Claims 1 to 10, characterized in that the diameters of the side port holes are the same.

12. The neural transplantation device according to any one of Claims 1 to 11, characterized in that the diameter of each side port hole (15A),(15B) is 0.3 mm.

13. The neural transplantation device according to any one of Claims 1 to 12, characterized in that the microinjector (1) is manufactured from acetal nylon and ionized aluminum.

14. The neural transplantation device according to any one of Claims 1 to 13, characterized in that the cannula (2) is manufactured from stainless steel.

15. A method of using a neural transplantation device defined according to any one of Claims 2 to 14 for administering an injection, comprising the steps of:
- positioning the syringe plunger (12) in an initial upward position;
- positioning the syringe barrel (7) with attached guide nut (8) in an essentially unwound position inside the cylindrical barrel (5) of the sleeve (4) of the microinjector (1);
- rotating the driving means to advance the syringe plunger (12) in a downward axial direction through the syringe barrel (7) thereby aspirating and depositing a portion of the contents of the syringe barrel (7) through the side port holes (15A),(15B) of the cannula (2);
- rotating the guide nut (8) to effectively withdraw the

syringe (3) and cannula (2) in an upward axial direction at a predetermined distance away from a previous neural target site; and

- repeating steps involving rotating the driving means to deliver a portion of the contents of the syringe barrel (7) and rotating the guide nut (8) to reposition the cannula (2), thereby resulting in sequential delivery of multiple portions of the contents of the syringe barrel (7) in a three-dimensional spiral array per single trajectory at a predetermined neural target site.

16. The method according to Claim 15, characterized in that the driving means comprises a plunger driver (11) and a drive nut (10).

17. The method according to Claim 16, characterized in that the plunger driver (11) is adapted to cooperate with the proximal end of the syringe plunger (12) and the distal end of the drive nut (10) is engaged with the proximal end of the plunger driver (11), such that rotation of either the drive nut (10) or plunger driver (11) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and syringe plunger (12).

18. The method according to Claim 16 or 17, characterized in that an exterior wall of the longitudinal cylindrical sleeve (4) and an interior wall of the plunger driver (11) and the drive nut (10) are threaded such that rotation of either the drive nut (10) or plunger driver (11) relative to the cylindrical sleeve (4) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and the syringe plunger (12).

19. A bullet guide (16) for use in combination with a stereotactic frame which functions as a mechanical guiding

system for the neural transplantation cannula according to any one of Claims 1 to 14, comprising:

- a top member (17) comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes (19A) sized to accommodate the insertion of the cannula (2); and
- a bottom member (20) comprising a hollow cylindrical element of the same diameter as the top member (17) but having a longer longitudinal axis; said bottom member (20) being closed at both ends and each end having an array of equidistantly spaced holes (21A),(21B) sized to accommodate the insertion of the cannula (2);
- characterized in that the top member (17) and bottom member (20) are mounted in spaced coaxial alignment in the stereotactic frame with the respective arrays of holes (19A),(21A),(21B) in mutual alignment to guide deployment of the cannula (2) through an aligned set of said holes (19A),(21A),(21B) to a predetermined cerebral target.

20. The bullet guide (16) according to Claim 16, characterized in that the top member (17) and bottom member (20) are manufactured from acetal nylon.

minimal number of penetrations into the host brain.

Another object of the present invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, which permits the precise placement of a predetermined amount of neural cells or tissue to a targeted site in a subject.

Another object of the invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, that can be easily incorporated with a syringe to facilitate reliable and safe neural transplantation of cell grafts to the human brain.

A further object of the invention is to provide a delivery system for neural transplantation grafts, comprising a microinjector and transplantation cannula, which in combination with a syringe, are designed to minimize implantation tissue trauma and maximize the number of graft deposits per injection using a unique spiral technique.

Still another object of the invention is to provide a bullet guide which, when mounted to a stereotactic frame, functions as a mechanical guiding system for the transplantation cannula thereby permitting multiple access of the cannula without adjusting or disturbing the frame.

According to one aspect of the invention there is provided a neural transplantation device for use in combination with a syringe, including a syringe barrel and plunger, comprising:

- a microinjector adapted for connection to a proximal end of a syringe barrel and in cooperation with a syringe plunger for effecting incremental depression of the plunger; and
- a cannula adapted for connection to a distal end of the syringe barrel, said cannula having a single passageway with

an open upper end and a lower end defining a blunt closed tip and having a pair of side port holes that are diametrically opposed and slightly offset to each other near the vicinity of the cannula tip;

- whereby upon placement of the cannula at a predetermined targeted neural site, the microinjector is capable of effecting incremental depression of the plunger to result in a metered delivery of the contents of the syringe barrel through the cannula port holes at the targeted site.

A particular embodiment provides a neural transplantation device, characterized in that the microinjector comprises:

- a longitudinal hollow cylindrical sleeve extending into a cylindrical barrel of larger diameter at the distal end thereof, said sleeve capable of receiving a syringe plunger;
- a guide nut rotatably adjustable within the cylindrical barrel and adapted to cooperate with the proximal end of the syringe barrel; and
- a driving means rotatably mounted near the proximal end of the cylindrical sleeve and adapted to cooperate with the syringe plunger;
- whereby operation of the microinjector in combination with the syringe and the cannula allows delivery of an injection such that rotation of the driving means renders a downward axial force to the plunger of the syringe thereby aspirating contents of the syringe barrel through the side port holes of the cannula; while rotation of the guide nut in the opposite direction moves the syringe in an upward axial direction to reposition the cannula; and rotation of the driving means and the guide nut in a repeated manner facilitates sequential delivery of multiple portions of the contents of the syringe barrel along a single trajectory in a three-dimensional spiral array at a predetermined neural injection site.

According to another aspect of the invention, there is

provided a method of using the neural transplantation device for administering an injection, comprising the steps of:

- positioning the syringe plunger in an initial upward position;
- positioning the syringe barrel with attached guide nut in an essentially unwound position inside the cylindrical barrel of the sleeve of the microinjector;
- rotating the driving means to advance the syringe plunger in a downward axial direction through the syringe barrel thereby aspirating and depositing a portion of the contents of the syringe barrel through the side port holes of the cannula;
- rotating the guide nut to effectively withdraw the syringe and cannula in an upward axial direction at a predetermined distance away from a previous neural target site; and
- repeating steps involving rotating the driving means to deliver a portion of the contents of the syringe barrel and rotating the guide nut to reposition the cannula, thereby resulting in sequential delivery of multiple portions of the contents of the syringe barrel in a three-dimensional spiral array per single trajectory at a predetermined neural target site.

Yet according to another aspect of the invention, there is provided a bullet guide for use in combination with a stereotactic frame which functions as a mechanical guiding system for the neural transplantation cannula, the bullet guide comprising:

- a top member comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes sized to accommodate the insertion of the cannula; and
- a bottom member comprising a hollow cylindrical element of the same diameter as the top member but having a longer longitudinal axis; said bottom member being closed at both ends and each end having an array of equidistantly spaced holes sized to accommodate the insertion of the cannula;

- characterized in that the top member and bottom member are mounted in spaced coaxial alignment in the stereotactic frame with the respective arrays of holes in mutual alignment to guide deployment of the cannula through an aligned set of said holes to a predetermined cerebral target.

Thus, the present invention affords a microinjector and transplantation cannula adapted and designed for use, for instance, with a 50 μl Hamilton syringe. The Hamilton syringe comprises a syringe barrel, which receives fluid contents, and a rod-like plunger for expelling the fluid contents from the barrel. In the assembled relationship, the microinjector and cannula create a secure and cooperative attachment to the extreme proximal and distal ends, respectively, of a Hamilton syringe, such that all the components are coaxially aligned to one another.

The microinjector essentially comprises a longitudinal cylindrical sleeve which is threaded on its exterior surface and extends abruptly into a plunger guide at its distal end that has a larger diameter than the sleeve. The exterior surface of the plunger guide is uniform and its internal diameter is sized to fit and cooperate with the peripheral shoulder of the barrel of a syringe. The inner wall of the plunger guide is threaded to match and interface with a guide nut which is adjustably rotated inside the barrel. The guide nut is a small hollow cylindrical spool with a collar at its extreme distal end that acts as a lower boundary stop to limit its position inside the plunger guide when fully wound. In turn, the guide nut is designed to securely interface with the syringe immediately beneath the peripheral shoulder located at the extreme proximal end of the barrel. Accordingly, attaching the guide nut to the barrel converts the syringe to an adjustably rotated device that can easily be wound inside the plunger guide. Therefore, rotating the guide nut in

either a clockwise or counter-clockwise direction simultaneously rotates the syringe in the same direction. Depending on the direction of rotation, this operation ultimately translates into either an upward or downward vertical movement of the syringe. Therefore, the vertical distance in which the syringe moves by rotation of the guide nut is a function of the length and diameter of the plunger guide and guide nut.

Mounted at the proximal end of the cylindrical sleeve is a driving means comprising a threaded drive nut engaged with a threaded plunger driver which are both adjustably rotated in either a clockwise or counter-clockwise direction. As a result of their connection, rotating one element moves the other element simultaneously. The plunger driver is engaged with the proximal end of a syringe plunger such that when the driver

Mounted at the proximal end of the cylindrical sleeve (4) is a driving means comprising a threaded drive nut (10) engaged with a threaded plunger driver (11) which are both adjustably rotated in either a clockwise or counter-clockwise direction. As a result of their connection, rotating either the drive nut (10) or plunger driver (11) moves the other element simultaneously. The plunger driver (11) is engaged with the proximal end of a syringe plunger (12) such that when the driver (11) is rotated, the movement of the plunger (12) is controlled in either an upward or downward direction along a longitudinal axis parallel to the syringe (3). Therefore, during neural transplantation, rotation of the plunger driver (11) results in delivery of a desired volume of cell suspension contained within the syringe barrel (7).

The transplantation cannula (2) is a long narrow needle provided with a standard Luer lock (13) at its proximal end. The Luer lock (13) allows the cannula (2) to be readily attached to and in fluid connection with the contents of the syringe (3), and then easily removed following use. The tip of the cannula (2) at the extreme distal end (14) is closed and its outer surface has been rounded and polished in a semi-spherical shape to minimize trauma to neural tissue upon insertion. As shown in Figure 2, located near the tip of the cannula are a pair of holes, (15A) and (15B), to allow egress of cells during aspiration of the syringe (3) and which are diametrically opposed and slightly offset to one another. In the embodiment shown, hole (15B) is located 1.0 mm from the cannula tip (14) and hole (15A) is offset from hole (15B) by a distance of 2.0 mm.

The bullet guide (16), illustrated in Figure 3, comprises both a top portion and a bottom portion that are mounted to a stereotactic frame and function as a mechanical guiding system for the transplantation cannula (2). The top

suspension, the guide nut (8) is rotated 90° in a clockwise position thereby withdrawing the syringe (3) and cannula (2) in an upward vertical direction at a predetermined distance away from the first target site. Aspiration and delivery of the second volume of cell suspension is made by repeating the operation involving rotation of the plunger driver (11). Sequential repetition of the steps involving rotation of the plunger driver (11) and guide nut (8) to deliver the contents of the syringe (3) and reposition the cannula (2), respectively, allows several injections to be made thereby distributing the cells in a three-dimensional spiral array within the brain tissue.

Figures 6A and 6B provide front and top views, respectively, of a sequence of four injections, 3.0 mm apart, made in a single trajectory. The first injection delivers two graft deposits oriented opposite to each other and one at a slightly higher level than the other (solid balls). The cannula (2) is then withdrawn 3.0 mm in a stepwise fashion and rotated 90° clockwise and so that another two deposits can be made (solid balls). The process is repeated two more times until a total of 8 deposits are made per trajectory resulting in a three-dimensional spiral array.

Additional cell deposits at different trajectories are made by removing the microinjector (1) from its operative position, governed by the square grids, (19) and (21), of the bullet guide (16), and then reinserting the transplantation cannula (2) of the microinjector (1) through another specified landmark of holes contained within the grids (19) and (21).

Although only one exemplary embodiment of this invention has been described in detail above, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiment without materially departing from the

novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses are intended to cover the structures described herein as performing the recited function and not only structural equivalents, but also equivalent structures.

The following Examples illustrate the invention:

CLAIMS:

1. A neural transplantation device for use in combination with a syringe (3), including a syringe barrel (7) and plunger (12), comprising:
- a microinjector (1) adapted for connection to a proximal end of a syringe barrel (7) and in cooperation with a syringe plunger (12) for effecting incremental depression of the plunger (12); and
- a cannula (2) adapted for connection to a distal end of the syringe barrel (7), said cannula (2) having a single passageway with an open upper end and a lower end defining a blunt closed tip (14) and having a pair of side port holes (15A),(15B) that are diametrically opposed and slightly offset to each other near the vicinity of the cannula tip (14);
- whereby upon placement of the cannula (2) at a predetermined targeted neural site, the microinjector (1) is capable of effecting incremental depression of the plunger (12) to result in a metered delivery of the contents of the syringe barrel (7) through the cannula port holes (15A),(15B) at the targeted site.

2. The neural transplantation device according to Claim 1, characterized in that the microinjector (1) comprises:
- a longitudinal hollow cylindrical sleeve (4) extending into a cylindrical barrel (5) of larger diameter at the distal end thereof, said sleeve (4) capable of receiving a syringe plunger (12);
- a guide nut (8) rotatably adjustable within the cylindrical barrel (5) and adapted to cooperate with the proximal end of the syringe barrel (7); and
- a driving means rotatably mounted near the proximal end of the cylindrical sleeve (4) and adapted to cooperate with

the syringe plunger (12);
- whereby operation of the microinjector (1) in combination with the syringe (3) and the cannula (2) allows delivery of an injection such that rotation of the driving means renders a downward axial force to the plunger (12) of the syringe (3) thereby aspirating contents of the syringe barrel (7) through the side port holes (15A),(15B) of the cannula (2); while rotation of the guide nut (8) in the opposite direction moves the syringe (3) in an upward axial direction to reposition the cannula (2); and rotation of the driving means and the guide nut (8) in a repeated manner facilitates sequential delivery of multiple portions of the contents of the syringe barrel (7) along a single trajectory in a three-dimensional spiral array at a predetermined neural injection site.

3. The neural transplantation device according to Claim 2, characterized in that the guide nut (8) is a small hollow cylindrical spool with a collar (9) at its extreme distal end that acts as a lower boundary stop to limit its position inside the cylindrical barrel (5) when fully wound inside.

4. The neural transplantation device according to Claim 2 or 3, characterized in that an exterior wall of the guide nut (8) and an interior wall of the cylindrical barrel (5), which receives the guide nut (8), are threaded such that rotation of the guide nut (8) relative to the cylindrical barrel (5) causes a corresponding linear, axial movement of the guide nut (8) through the cylindrical barrel (5).

5. The neural transplantation device according to any one of Claims 2 to 4, characterized in that the driving means comprises a plunger driver (11) and a drive nut (10).

6. The neural transplantation device according to Claim 5, characterized in that the plunger driver (11) is adapted to cooperate with the proximal end of the syringe plunger (12) and a distal end of the drive nut (10) is engaged with a proximal end of the plunger driver (11), such that rotation of either the drive nut (10) or plunger driver (11) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and syringe plunger (12).

7. The neural transplantation device according to Claim 5 or 6, characterized in that an exterior wall of the longitudinal cylindrical sleeve (4) and an interior wall of the plunger driver (11) and the drive nut (10) are threaded such that rotation of either the plunger driver (11) or drive nut (10) relative to the cylindrical sleeve (4) causes a corresponding linear, axial movement of the plunger driver (11), drive nut (10), and the syringe plunger (12).

8. The neural transplantation device according to any one of Claims 1 to 7, characterized in that the cannula (2) has a length sufficient to linearly penetrate and enter a host brain such that the pair of side port holes (15A),(15B) is concurrently positionable at a predetermined targeted site within the host brain.

9. The neural transplantation device according to any one of Claims 1 to 8, characterized in that the cannula (2) has an outside diameter of about 0.8 mm.

10. The neural transplantation device according to any one of Claims 1 to 9, characterized in that the side port holes (15A),(15B) are positioned such that the distances between a distal edge of a first (15B) and a second side

port hole (15A) to the cannula tip (14) are about 1.0 mm and 3.0 mm, respectively.

11. The neural transplantation device according to any one of Claims 1 to 10, characterized in that the diameters of the side port holes are the same.

12. The neural transplantation device according to any one of Claims 1 to 11, characterized in that the diameter of each side port hole (15A),(15B) is 0.3 mm.

13. The neural transplantation device according to any one of Claims 1 to 12, characterized in that the microinjector (1) is manufactured from acetal nylon and ionized aluminum.

14. The neural transplantation device according to any one of Claims 1 to 13, characterized in that the cannula (2) is manufactured from stainless steel.

15. A method of using a neural transplantation device defined according to any one of Claims 2 to 14 for administering an injection, comprising the steps of:
- positioning the syringe plunger (12) in an initial upward position;
- positioning the syringe barrel (7) with attached guide nut (8) in an essentially unwound position inside the cylindrical barrel (5) of the sleeve (4) of the microinjector (1);
- rotating the driving means to advance the syringe plunger (12) in a downward axial direction through the syringe barrel (7) thereby aspirating and depositing a portion of the contents of the syringe barrel (7) through the side port holes (15A),(15B) of the cannula (2);
- rotating the guide nut (8) to effectively withdraw the

syringe (3) and cannula (2) in an upward axial direction at a predetermined distance away from a previous neural target site; and

- repeating steps involving rotating the driving means to deliver a portion of the contents of the syringe barrel (7) and rotating the guide nut (8) to reposition the cannula (2), thereby resulting in sequential delivery of multiple portions of the contents of the syringe barrel (7) in a three-dimensional spiral array per single trajectory at a predetermined neural target site.

16. The method according to Claim 15, characterized in that the driving means comprises a plunger driver (11) and a drive nut (10).

17. The method according to Claim 16, characterized in that the plunger driver (11) is adapted to cooperate with the proximal end of the syringe plunger (12) and the distal end of the drive nut (10) is engaged with the proximal end of the plunger driver (11), such that rotation of either the drive nut (10) or plunger driver (11) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and syringe plunger (12).

18. The method according to Claim 16 or 17, characterized in that an exterior wall of the longitudinal cylindrical sleeve (4) and an interior wall of the plunger driver (11) and the drive nut (10) are threaded such that rotation of either the drive nut (10) or plunger driver (11) relative to the cylindrical sleeve (4) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and the syringe plunger (12).

19. A bullet guide (16) for use in combination with a stereotactic frame which functions as a mechanical guiding

system for the neural transplantation cannula according to any one of Claims 1 to 14, comprising:

- a top member (17) comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes (19A) sized to accommodate the insertion of the cannula (2); and
- a bottom member (20) comprising a hollow cylindrical element of the same diameter as the top member (17) but having a longer longitudinal axis; said bottom member (20) being closed at both ends and each end having an array of equidistantly spaced holes (21A),(21B) sized to accommodate the insertion of the cannula (2);
- characterized in that the top member (17) and bottom member (20) are mounted in spaced coaxial alignment in the stereotactic frame with the respective arrays of holes (19A),(21A),(21B) in mutual alignment to guide deployment of the cannula (2) through an aligned set of said holes (19A),(21A),(21B) to a predetermined cerebral target.

20. The bullet guide (16) according to Claim 16, characterized in that the top member (17) and bottom member (20) are manufactured from acetal nylon.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

CLAIMS:

1. (New) A neural transplantation device for use in combination with a syringe (3), including a syringe barrel (7) and plunger (12), comprising:
- a microinjector (1) adapted for connection to a proximal end of a syringe barrel (7) and in cooperation with a syringe plunger (12) for effecting incremental depression of the plunger (12); and
- a cannula (2) adapted for connection to a distal end of the syringe barrel (7), said cannula (2) having a single passageway with an open upper end and a lower end defining a blunt closed tip (14) and having a pair of side port holes (15A),(15B) that are diametrically opposed and slightly offset to each other near the vicinity of the cannula tip (14);
- whereby upon placement of the cannula (2) at a predetermined targeted neural site, the microinjector (1) is capable of effecting incremental depression of the plunger (12) to result in a metered delivery of the contents of the syringe barrel (7) through the cannula port holes (15A),(15B) at the targeted site.

2. (New) The neural transplantation device according to Claim 1, characterized in that the microinjector (1) comprises:
- a longitudinal hollow cylindrical sleeve (4) extending into a cylindrical barrel (5) of larger diameter at the distal end thereof, said sleeve (4) capable of receiving a syringe plunger (12);
- a guide nut (8) rotatably adjustable within the cylindrical barrel (5) and adapted to cooperate with the proximal end of the syringe barrel (7); and
- a driving means rotatably mounted near the proximal end of

the cylindrical sleeve (4) and adapted to cooperate with the syringe plunger (12);

- whereby operation of the microinjector (1) in combination with the syringe (3) and the cannula (2) allows delivery of an injection such that rotation of the driving means renders a downward axial force to the plunger (12) of the syringe (3) thereby aspirating contents of the syringe barrel (7) through the side port holes (15A), (15B) of the cannula (2); while rotation of the guide nut (8) in the opposite direction moves the syringe (3) in an upward axial direction to reposition the cannula (2); and rotation of the driving means and the guide nut (8) in a repeated manner facilitates sequential delivery of multiple portions of the contents of the syringe barrel (7) along a single trajectory in a three-dimensional spiral array at a predetermined neural injection site.

3. (New) The neural transplantation device according to Claim 2, characterized in that the guide nut (8) is a small hollow cylindrical spool with a collar (9) at its extreme distal end that acts as a lower boundary stop to limit its position inside the cylindrical barrel (5) when fully wound inside.

[3.]4. (Amended) The neural transplantation device according to Claim 2 or 3, characterized in that an exterior wall of the guide nut (8) and an interior wall of the cylindrical barrel (5), which receives the guide nut (8), are threaded such that rotation of the guide nut (8) relative to the cylindrical barrel (5) causes a corresponding linear, axial movement of the guide nut (8) through the cylindrical barrel (5).

VERSION WITH MARKINGS TO SHOW CHANGES MADE

5. (New) The neural transplantation device according to any one of Claims 2 to 4, characterized in that the driving means comprises a plunger driver (11) and a drive nut (10).

6. (New) The neural transplantation device according to Claim 5, characterized in that the plunger driver (11) is adapted to cooperate with the proximal end of the syringe plunger (12) and a distal end of the drive nut (10) is engaged with a proximal end of the plunger driver (11), such that rotation of either the drive nut (10) or plunger driver (11) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and syringe plunger (12).

[4.]7. (Amended) The neural transplantation device according to Claim [2 or 3]5 or 6, characterized in that an exterior wall of the longitudinal cylindrical sleeve (4) and an interior wall of the plunger driver (11) and the drive nut (10) are threaded such that rotation of either the plunger driver (11) or drive nut (10) relative to the cylindrical sleeve (4) causes a corresponding linear, axial movement of the plunger driver (11), drive nut (10), and the syringe plunger (12).

[5.]8. (Amended) The neural transplantation device according to any one of Claims 1 to [4]7, characterized in that the cannula (2) has a length sufficient to linearly penetrate and enter a host brain such that the pair of side port holes (15A), (15B) is concurrently positionable at a predetermined targeted site within the host brain.

[6.]9. (Amended) The neural transplantation device according to any one of Claims 1 to [5]8, characterized in that the cannula (2) has an outside diameter of about 0.8 mm.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

[7.]10. (Amended) The neural transplantation device according to any one of Claims 1 to [6]9, characterized in that the side port holes (15A), (15B) are positioned such that the distances between a distal edge of a first (15B) and a second side port hole (15A) to the cannula tip (14) are about 1.0 mm and 3.0 mm, respectively.

[8.]11. (Amended) The neural transplantation device according to any one of Claims 1 to [7]10, characterized in that the diameters of the side port holes are the same.

[9.]12. (Amended) The neural transplantation device according to any one of Claims 1 to [8]11, characterized in that the diameter of each side port hole (15A), (15B) is 0.3 mm.

[10.]13. (Amended) The neural transplantation device according to any one of Claims 1 to [9]12, characterized in that the microinjector (1) is manufactured from acetal nylon and ionized aluminum.

[11.]14. (Amended) The neural transplantation device according to any one of Claims 1 to [10]13, characterized in that the cannula (2) is manufactured from stainless steel.

15. (New) A method of using a neural transplantation device defined according to any one of Claims 2 to 14 for administering an injection, comprising the steps of:
- positioning the syringe plunger (12) in an initial upward position;
- positioning the syringe barrel (7) with attached guide nut (8) in an essentially unwound position inside the cylindrical

barrel (5) of the sleeve (4) of the microinjector (1);
- rotating the driving means to advance the syringe plunger (12) in a downward axial direction through the syringe barrel (7) thereby aspirating and depositing a portion of the contents of the syringe barrel (7) through the side port holes (15A),(15B) of the cannula (2);
- rotating the guide nut (8) to effectively withdraw the syringe (3) and cannula (2) in an upward axial direction at a predetermined distance away from a previous neural target site; and
- repeating steps involving rotating the driving means to deliver a portion of the contents of the syringe barrel (7) and rotating the guide nut (8) to reposition the cannula (2), thereby resulting in sequential delivery of multiple portions of the contents of the syringe barrel (7) in a three-dimensional spiral array per single trajectory at a predetermined neural target site.

16. (New) The method according to Claim 15, characterized in that the driving means comprises a plunger driver (11) and a drive nut (10).

17. (New) The method according to Claim 16, characterized in that the plunger driver (11) is adapted to cooperate with the proximal end of the syringe plunger (12) and the distal end of the drive nut (10) is engaged with the proximal end of the plunger driver (11), such that rotation of either the drive nut (10) or plunger driver (11) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and syringe plunger (12).

18. (New) The method according to Claim 16 or 17, characterized in that an exterior wall of the longitudinal

cylindrical sleeve (4) and an interior wall of the plunger driver (11) and the drive nut (10) are threaded such that rotation of either the drive nut (10) or plunger driver (11) relative to the cylindrical sleeve (4) causes a corresponding linear, axial movement of the drive nut (10), plunger driver (11), and the syringe plunger (12).

19. (New) A bullet guide (16) for use in combination with a stereotactic frame which functions as a mechanical guiding system for the neural transplantation cannula according to any one of Claims 1 to 14, comprising:
- a top member (17) comprising a hollow cylindrical element having a closed end with an array of equidistantly spaced holes (19A) sized to accommodate the insertion of the cannula (2); and
- a bottom member (20) comprising a hollow cylindrical element of the same diameter as the top member (17) but having a longer longitudinal axis; said bottom member (20) being closed at both ends and each end having an array of equidistantly spaced holes (21A),(21B) sized to accommodate the insertion of the cannula (2);
- characterized in that the top member (17) and bottom member (20) are mounted in spaced coaxial alignment in the stereotactic frame with the respective arrays of holes (19A),(21A),(21B) in mutual alignment to guide deployment of the cannula (2) through an aligned set of said holes (19A),(21A),(21B) to a predetermined cerebral target.

20. (New) The bullet guide (16) according to Claim 16, characterized in that the top member (17) and bottom member (20) are manufactured from acetal nylon.